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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,507	09/29/2005	Kazumasa Hamamura	2007_0364	4233

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NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,507	HAMAMURA ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *38-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,11,13,14,16-18,23 and 30-37* is/are rejected.

7)☒ Claim(s) *8,9,12,15,19-22 and 24-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-44 are pending in the instant application and **Claims 45-51** are canceled. **Claims 38-44** are withdrawn from further consideration and **Claims 1, 9, 13, 17-20, 24, 26, 28 & 30** are currently amended.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 06/10/2005 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Specification

The disclosure is objected to because of the following informalities: the specification is missing a reference to the deposited material; *see* MPEP 2411.05 & 37 CFR 1.809(d). Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 10, 11, 13, 14, 16-18 & 30 are rejected under 35 U.S.C. 102(a & e) as being anticipated by Commons *et al.* (WO 03/000649 A1, *see* IDS). Described in the international application on pages 4-5 is a formula wherein **A** = optionally substituted bicyclic aromatic fused ring; $\mathbf{M^3}$ = bond; $\mathbf{X^2}$ = O; $\mathbf{M^4}$ = CHR_5; $\mathbf{R^1}$ = H; $\mathbf{M^2}$ = CH2; **Y** = C(=O)-N(R3)-; $\mathbf{X^1}$ = O; $\mathbf{R^2}$ = optionally substituted aromatic group; & **R** = R_7 on page 4.

Claim Rejections - 35 USC § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

I) Claims 1, 6, 7, 18 & 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound according to formulae (I) & (I') wherein: **A** = *some*, specific aromatic rings or bicyclic aromatic rings, (outlined below), it does not reasonably provide enablement for a compound having *any* aromatic ring envisaged.

II) Claims 31-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for a *therapeutic agent* comprising a compound of formula (I), (as outlined herein), or pharmaceutically acceptable salts thereof, it does not

reasonably provide enablement for a *prophylactic agent* thereof, (and therefore not enabling for the broadest term "agent", i.e. **Claim 36**).

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) *The breadth of the claims;*
(B) *The nature of the invention;*
(C) *The state of the prior art;*
(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*
(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The breadth of the claims & The nature of the invention

The currently pending invention is drawn to compounds and pharmaceutical agents according to formula (I), wherein the definitions of **X^1, X^2, A, Y, M^1-M^4, R^1 & R^2** are defined in **Claim 1**. Compounds according to this formula are useful for regulating the nuclear receptor PPAR and treating diseases encompassed via that mechanism of action. During examination, the claims are given the broadest reasonable interpretation consistent with the specification; therefore, the breadth of variable **A** includes *any* monocyclic or bicyclic aromatic ring; i.e., those listed on pages 31-32 in the

specification. Further, it is understood that diseases associated with the nuclear receptor PPAR are treatable, however, it has not been established that the same group of diseases are preventable. These claims are too broad because they are not supported by the original disclosure: undue breadth.

The state of the prior art & The level of predictability in the art

I) The synthesis of complex products is an integral part of modern organic chemistry. Examination of many synthetic endeavors, large and small, reveals that the substitution of the core ring **A** from benzene or thiazole, for example, to other aromatic rings changes the necessary starting materials for making these compounds as well as the predictability of their chemical reactivity and pharmaceutical utility.

The core difference influences the bond length, electronegativity, and therefore the localization of electrons with respect to the aromatic component. A change within the structural core results in a lack of predictability in preparation and reactivity. The prior art is silent with respect to the predictability of *any* compound as set forth by the formula (I) in with respect to its preparation, isolation, and use for treatments. A change in **A** would not only effect the chemical properties of the reagents for producing the desired products, but inherently also effects the desired biological properties for this class of compounds. Therefore, it is unpredictable to know, from the outlined methods in the instant specification, how to make and use *all* of the compounds claimed in the formula (I).

In the instant case, a review of the literature provided by Applicant in the Information Disclosure Statement (IDS) and the literature acquired via a commercial database (Registry/Caplus) structure search performed by Examiner suggests that the state of the prior art is more advanced for species in which the structural core consists of **A** = phenyl, thiophene, furan, benzofuran, benzothiophene, benzimidazole, and naphthalene. However, the prior art is silent pertaining to other structural cores: no species have been described for this class of compounds wherein **A** = pyrazole, pyrrole, imidazole, pyrimidine, for example, suggesting that it is not known how to make and use *all* of the claimed subject matter.

II) Drug design is the approach of finding drugs by design, based on their biological targets. Typically a drug target is a key molecule involved in a particular metabolic or signalling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen. Some approaches attempt to stop the functioning of the pathway in the diseased state by causing a key molecule to stop functioning. Drugs may be designed that bind to the active region and inhibit this key molecule. However these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules. Other approaches may be to enhance the normal pathway by promoting specific molecules in the normal pathways that may have been affected in the diseased state. The structure of the drug molecule that can specifically interact with the biomolecules can be modeled using computational tools. These tools can allow a drug

molecule to be constructed within the biomolecule using knowledge of its structure and the nature of its active site. Construction of the drug molecule can be made inside out or outside in depending on whether the core or the R-groups are chosen first.

Highly sophisticated tools for rational drug design still have not taken the unpredictability out of this complex art; it still requires trial and error experimentation. The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compositions may provide a *treatment* for PPAR-related diseases, but it does not mean that the same group of compositions may *prevent* a PPAR-related diseases. Since these obstacles establish that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face, a substantial amount of biological data

and correlative information is required to enable the skilled artisan to use the invention as claimed.

At the time of filing, the use of small molecule therapeutics to treat diseases associated with the PPAR receptor was known. However, the list of diseases outlined in **Claim 37** is not supported by the disclosure, and therefore the broad term "PPAR-related diseases" in **Claim 32** is not supported either. For instance, it is documented in the literature that the use of PPAR receptor modulators are useful for the treatment of obesity, diabetes, arteriosclerosis, and the like, (the drug troglitazone is marketed for the treatment of diabetes; also *see* Hsueh *et al. Arterioscler. Thromb. Vasc. Biol.* **2001**, 1891-5; Duriez *et al. Exp. Opin. Invest. Drugs* **1998**, *7(11)*, pages 1997-2009); however, it is not apparent that PPAR receptor modulators are useful for the treatment of ketosis, acidosis, sexual dysfunction, cutaneous diseases, arthropathy, osteopenia, thrombotic diseases, dyspepsia, memory and learning disorders, hypertension, edema, lipoatrophy, insulinoma, lipotoxicity, and cancer. For example, the publication by Rumi *et al.* (*Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4(6)*, 465-477) demonstrates the uncertainty between the involvement of PPAR and cancer. This post-filing reference states that much is still left to be uncovered to clear the way for the use of PPAR receptor modulators in the treatment of cancer; therefore, it would certainly be an undue burden for someone of skill in the art to use the invention as claimed herein for the treatment of cancer.

The amount of direction/guidance & the presence/absence of working examples

I) The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed invention commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of *all* compounds according to formula (I) in which **A** = monocyclic or bicyclic aromatic rings. The direction provided does not adequately represent the scope of **Claim 1** as written. The Examiner points out that all of the compounds in the schemes and as well as the synthetic procedures described in the specification, (*see* examples on pages 339-447), provide guidance to the invention only when **A** = benzene, oxazoles, thiazole, benzothiophene, benzofuran, benzimidazole, and naphthalene. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that any compound of formula (I) would indeed be able to be synthesized and used by means of the methods outlined in the specification.

II) Applicant states, "Compound (I) of the present invention and a pharmaceutically acceptable salt thereof show excellent preventing and treating action for PPAR-related diseases...", (*see* specification on pages 451-2). Further, biological studies are outlined on pages 147-169. However, no evidence that a compound according to formula (I) is useful for preventing diseases is shown.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

I) In view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of formula (I) as defined. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. Undue experimentation would include, for instance: the preparation of multiple synthetic outlines for each of the different definitions of **A**; the preparation of the necessary starting materials required for each of the compounds according to the formula (I) wherein **A** is a distinct aromatic structure; followed by attempts to prepare a desired product for each of the different structural core, subsequently followed by isolation, characterization, and testing the various compounds to determine if indeed they had utility for the treatment of various diseases.

II) Claims 31-37 are drawn to pharmaceutical agents for the treatment and/or prophylaxis of a PPAR-related disease. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, demonstrate that if the identified subject did not develop the disease, and show that such an effect was the direct result of administration of the claimed invention. In order to treat a disease, one would need to identify which species (compound/composition) claimed herein has the desired effect as outlined for the biological pathways, and determine which disease the species is useful for treating.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. This rejection may be overcome by canceling **Claim 32**, amending **Claims 31 & 33-37** to state only "A therapeutic agent," and deletion of the unsupported diseases listed in **Claim 37**.

Claim Objections

Claims 8, 9, 12, 15, 19-22 & 24-29 are objected to as being dependent upon a rejected base **Claim 1**.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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